PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 November 2000 (29.11.00)	
International application No. PCT/CA00/00469	**Applicant's or agent's file reference** DH/11830.59
International filing date (day/month/year) 03 May 2000 (03.05.00)	**Priority date** (day/month/year) 03 May 1999 (03.05.99)
Applicant BERGERON, Michel, G. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 November 2000 (09.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer F. Baechler Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

Copy for the Elected Office (EO/US)

PCT/CA00/00469

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DUBUC, Jean, H.
Goudreau Gage Dubuc
The Stock Exchange Tower
Suite 3400
800 Place Victoria
Montreal, Quebec H4Z 1E9
CANADA

Date of mailing (day/month/year)
31 octobre 2001 (31.10.01)

Applicant's or agent's file reference
DH/11830.59

IMPORTANT NOTIFICATION

International application No.
PCT/CA00/00469

International filing date (day/month/year)
03 mai 2000 (03.05.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
INFECTIO RECHERCHE INC.
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Ste-Foy, Quebec G1V 4M7
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
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2705, boul. Laurier
Bureau RC-709
Ste-Foy, Quebec G1V 4G2
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
P. Blanchet (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DUBUC, Jean H. et al.
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Stock Exchange Tower
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23 JUL 2001

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.07.2001
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
DH/11830.59	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00469	03/05/2000	03/05/1999

Applicant
INFECTIO RECHERCHE INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Gallego, A Tel.+49 89 2399-8102

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DH/11830.59		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00469	03/05/2000	03/05/1999

International Patent Classification (IPC) or national classification and IPC
A61K47/48

Applicant
INFECTIO RECHERCHE INC. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/11/2000	17.07.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized officer

Vogt, T

Telephone No. +49 89 2399 8477

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00469

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25	as originally filed				

Claims, No.:

1-23	as received on	20/06/2001	with letter of	20/06/2001	

Drawings, sheets:

1/15-15/15	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

I Amendments (Art. 41 PCT).

The applicant filed a new set of claims with the letter of 20.06.2001. The major amendment relates to the incorporation of claim 20 into claim 1. Minor amendments are made to claims 17 and 18 (incorporation of CD4).

Claims 22 and 23 were added.

Said amendments meet the requirements of Art. 41 (2) PCT.

II Priority (Art. 8 PCT).

The present application (with amended claim 1) validly claims the right to the filing date of CA application 2270600 (03.05.1999).

V Reasoned Statement. (Rule 66(2) PCT).

Subject matter of the present application.

The provision of a formulation comprising immunoliposomes optionally enclosing a drug for targeting an infectious agent which acquires at least one host membrane protein.

Cited prior art documents. (Rule 64(1) PCT).

D1: DESORMEAUX ET AL. (1995) ZBL. BAKT. 282, 225-231.
D2: PHILLIPS (1994) J. IMMUNOL. 152, 3168-3174.
D3: ZELPHATI ET AL. (1993) ANTISENSE RES. DEV. 3, 323-338.
D4: DESORMEAUX ET AL. (1998) J. DRUG TARGETING 6, 1-15.
D5: MARUYAMA ET AL. (10-1999) ADV. DRUG DELIV. REVIEWS 40, 89-102.
D6: MENEZES DE ET AL. (05-1999) J. LIPOSOME RES. 9, 199-228.
D7: LUNDBERG ET AL. (09-2000) INT. J. PHARMAC. 205, 101-108.
D8: BESTMAN-SMITH ET AL. (09-2000) BBA 1468, 161-174.
D9: BESTMAN-SMITH ET AL. (10-2000) AIDS 14, 2457-2465.
D10: DUFRESNE ET AL. (10-1999) BBA 1421, 284-294.
D11: US-A-5013556.
D12: EP-A-0286418.
D13: WO-A-9625147.
D14: WO-A-9610399. (cited in the description as US-A-5773027)

D15: WO-A-9610585.

D5, D6 and D10 will be considered as prior art according to Rule 33 (1) PCT insofar as they do not relate to the subject matter disclosed by the priority document.

D1 and D4 are reviews written by the authors of the present application relating to strategies using drugs loaded -liposomes (D1) and -immunoliposomes (D4) for the targeting of HIV infected tissues. D4 discloses the use of anti-CD4 antibodies conjugated to liposomes loaded with AZT to target to CD4+ lymphocytes (p. 6, 7). It further suggested to use these formulations for vaccinations, because of the observed increased immunogenecity in the presence of liposomes. D4 further contains references to the lipid composition of the liposomes (p. 3, l. 1-3), references to possible drugs to be enclosed in liposomes (p. 3, l. 40-43), discloses that sterically stabilized liposomes (eg. PEG-modified liposomes) increase the blood circulation time and visualizes the strategies in Figure 1.

D2 discloses anti-CD4 immunoliposomes optionally modified with PEG and optionally loaded with AZT to target to CD4+ PBMCs (peripheral blood mononuclear cells). The liposomes of the D2 are prepared from DPPC/DMPC (10/1) and are optionally substituted with 5% PEG_{1900}-PE (see materials and methods).

D3 discloses immunoliposomes loaded with antisense oligonucleotides to target to HIV infected T-lymphoblastoid cells. D3 discloses HLA-B and -C, CD7, and CD4 as possible targets for antibodies. (cf. p. 325; Antibodies, Cells and virus).
The examining authority is of the opinion that the subject matter of claims 1, 2, 10-18 and 22 does not meet the requirement of novelty over D3.

D5 relates to the use of loaded immunoliposomes to target cancer cells. It discloses that the pendant immunoliposome, also envisaged by the present application and illustrated in Fig. 1 of D4, is highly effective in targeting liposomes (Fig. 5).

D6 also relates to the use of loaded immunoliposomes to target cancer cells. It discloses the use of anti-CD19 antibodies, PEG, doxorubicin enclosed in the liposomes to target human B lymphoma cells. Because the disease cancer is not considered to be 'an infectious disease' D5 and D6 are not considered to be novelty destroying to the

present application.

D7, D8 and D9 are published after the filing date of the present application.

D10 discloses the subject matter covered by the priority document. Because it is the opinion of the examining authority that priority is validly claimed for this part of the application and D10 was published after (15.10.1999) the filing date of the priority document, the contents of D10 will be neglected.

D11 discloses sterically stabilized immunoliposomes for the targeting of HIV infected B or T cells. (cf. claims).

D12 discloses a method for targeting host cells infected by retroviruses (eg. HIV) using liposomes loaded with phosphorylated nucleotides (eg. AZT, DDC) and coated with an appropriate ligand (eg. anti-CD4). (cf. claims). The liposomes of D12 contain DPPC/DMPG in approximately 5/1 molar ratio.

D13 does not appear to contain information relevant to the present application.

D14 is written by the same inventors and discloses the lipid composition of the liposomes used in the present application.

D15 relates to the treatment of cancer with immunoliposomes.

Novelty and inventive step. (Art. 33(2,3) PCT).

As will have become clear from the above the idea of targeting liposomes that encapsulate drugs to specific tissues for the treatment of a disease is not novel. Also the idea of conjugating (parts of) antibodies to liposomes to increase the targeting efficiency thereof is not novel. Both, also apply for the application to infectious diseases such as AIDS.

However, none of the cited prior art documents mentions the use of ligands directed to HLA-DR. Therefore, claim 1 and all claims dependent thereon meet the requirement of novelty. (Rule 33 (2) PCT).

The technique as described in the present application and as first postulated almost two decades ago relies on the identification of an appropriate target on the outer-membrane leaflet of tissues (eg. a membrane protein). For the treatment of a disease this would imply membrane proteins directly or indirectly acquired as result thereof. About one decade ago it was discovered that the membrane protein HLA-DR is acquired as a result of HIV infection (see references 23, 24 in D8; 29 in D9 and p. 2 , l. 9-24 of the priority document). Hence it would appear that HLA-DR is an obvious target for such a strategy. However, despite the fact that the field of drug targetting has been booming over the last decade nobody has made the link towards the use of HLA-DR. Furthermore HLA-DR is a particular interesting target, because it is not only aquired by a host cell as a result of an infection it is also displayed by the infectious agent itself.

Hence, the subject matter of claims 1-21 of the present application meets the requirements of inventive step (Rule 33 (3) PCT).

Also the inventive step of claims 22 and 23 is acknowledged, based on the fact that the present application is the first to suggest the use of ligands that are aimed to target to a host cell receptor that is present on **both** the infected cell **and** the infectious agent.

Industrial applicability. (Art. 33(4) PCT).
The present application provides formulations for treatment of infectious diseases. The subject matter meets the requirement of industrial applicability.

VII Remarks related to the description (Art. 5 PCT).

The description should be brought into conformity with the amended claims.

The applicant should identify documents D2, D3, D4, D8, D9, D11 and D12 in the description. (Rule 5 PCT).

VIII Clarity of the claims (Art. 6 PCT).

Claims 7-9 are not conform the description on p. 7 and 8. The applicant is requested to amend the description or claims accordingly.

The vague and imprecise statement in the description on p. 25, l. 11-13 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

WHAT IS CLAIMED IS

1. A formulation for targeting an infectious agent which acquires a HLA-DR host membrane protein during its life cycle or a HLA-DR expressing host cell or both, said formulation comprising a ligand capable of binding to said host membrane protein, said ligand being coupled to a lipid-comprising vesicle.

2. A formulation according to claim 1 wherein lipid-comprising vesicle is a liposome.

3. A formulation according to claim 2 wherein said liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

4. A formulation according to claim 3, wherein said lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

5. A formulation according to claim 4, wherein the polyethyleneglycol has a molecular weight comprises between about 500 and 5000 daltons.

6 A formulation according to claim 3, wherein the molar ratio is 10:3.

7 A formulation according to claim 4 or 5, wherein said lipid component comprises a mixture of diacylphosphatidylcholine:diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10.3:0.1-3.

8. A formulation according to claim 2, 3 or 6, wherein said lipid component comprises a mixture of dipalmitoylphosphatidylcholine:dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or distearoylphosphatidylcholine:distearoylphosphatidylglycerol in a molar ratio of 10:3.

9. A formulation according to claim 2, 3, 4, 5 or 7, wherein said lipid component comprises a mixture of dipalmitoylphosphatidylcholine:dipalmitoylphosphatidylglycerol: dipalmitoylphosphatidylethanolamine-polyethyleneglycol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine:dipalmitoylphosphatidylglycerol:distearoylphosphatidylethanolamine-polyethyleneglycol in a molar ratio of 10:3.0.83.

10. A formulation according to any one of claims 1 to 9, wherein said host membrane protein further comprises one or more proteins selected from a histocompatibility complex protein, a membrane ATPase, thy-1, an interleukin receptor, annexin II, CD3 (T3), CD4 (T4), CD5 (T1), CD6 (T12), CD8 (T8), CD11a (LFA-1), CD11b (Mac-1), CD11c (gp150,95), CD1 (Lewis X), CD18, CD19, CD25 (Tac), CD30 (Ki-1), CD43 (leukosialin, sialophorin), CD44 (Pgp-1), CD48 (Blast-1), CD54 (ICAM-1), CD55 (DAF), CD59 (protectin, Mac inhibitor), CD63, CD71 (transferrin receptor), CDw108(GR2), cyclophilin A, cytoskeletal proteins and β_2-microglobulin

11. A formulation according to any one of claims 1 to 10, wherein said ligand is an antibody molecule selected from a whole antibody and an antibody fragment.

12. A formulation according to any one of claims 1 to 11, which comprises a drug effective against a disease or against the symptoms of a disease caused by said infectious agent.

13. A formulation according to any one of claims 1 to 11, wherein said host cell is a lymphoid cell or a cell of the reticuloendothelial system.

14. A formulation according to claim 12, wherein said host cell is a lymphoid cell or a cell of the reticuloendothelial system.

15 A formulation according to claim 13, wherein said infectious agent is HIV.

16. A formulation according to claim 14, wherein said infectious agent is HIV.

17. A formulation according to claim 13 or 15, wherein said host membrane protein further comprises one or more of CD4, MHC-I or CD54.

18 A formulation according to claim 14 or 16, wherein said host membrane protein further comprises one or more of CD4, MHC-I or CD54.

19. A formulation according to claim 12, 14, 16 or 18 wherein said drug is selected from AZT, ddI, ddC, 3TC, indinavir, saquinavir, ritonavir, nelfinavir, ganciclovir, foscarnet, ribavirin, amphotericin B and nystatin A.

20. A formulation according to any one of claims 1 to 19, wherein said ligand is an anti-Fab' antibody fragment directed against said host membrane protein.

21. The use of a formulation according to any one of claims 1 to 20 for treating or preventing a disease caused by said infectious agent.

22. The use of a ligand to a host membrane protein which is acquired by an infectious agent during its life cycle in the making of a formulation for targeting said infectious agent and its host cell, said ligand being coupled to a lipid-comprising vesicle and said protein does not consist of CD4 or of a HLA class 1 protein.

23. The use as defined in claim 22, wherein said formulation is defined in any one of claims 1 to 20.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 47/48

A2

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2,270,600 3 May 1999 (03.05.99) CA

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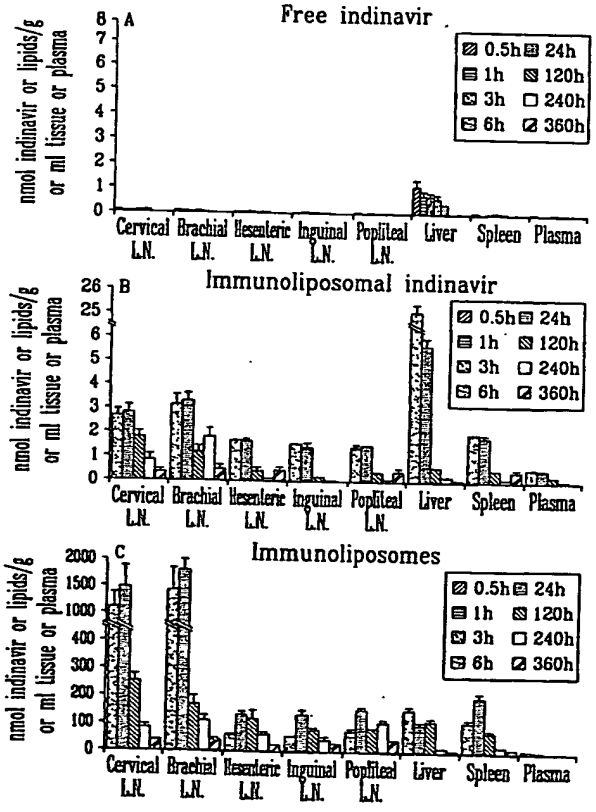
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METHODS AND FORMULATIONS FOR TARGETING INFECTIOUS AGENTS BEARING HOST CELL PROTEINS

(57) Abstract

A formulation is disclosed for the treatment of diseases caused by an infectious agent which acquires host membranes protein during its life cycle. The formulation is a targeting pharmaceutical composition. It comprises a ligand capable of binding the host membrane proteins coupled to a lipid–comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific liposomes bearing anti–HLA–DR or anti–CD4 antibodies comprising or not antiviral drugs, namely anti–HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.



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YU	Yugoslavia
ZW	Zimbabwe

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(19) World Intellectual Property Organization
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9 November 2000 (09.11.2000)

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(75) Inventors/Applicants *(for US only)*: **BERGERON, Michel, G.** [CA/CA]; 1145 des Erables, Quebec, Quebec G1R 2N4 (CA). **DESORMEAUX, André** [CA/CA]; 7640 de Beauchastel, Neufchatel, Quebec G2C 1Y1 (CA). **TREMBLAY, Michel, J.** [CA/CA]; 7073 rue des Brumes, Neufchatel, Quebec G2C 1P3 (CA).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
9 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/66173 A3

(54) Title: TARGETING OF INFECTIOUS AGENTS BEARING HOST CELL PROTEINS

(57) Abstract: A formulation is disclosed for the treatment of diseases caused by an infectious agent which acquires host membranes protein during its life cycle. The formulation is a targeting pharmaceutical composition. It comprises a ligand capable of binding the host membrane proteins coupled to a lipid-comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific liposomes bearing anti-HLA-DR or anti-CD4 antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/CA 00/00469

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DESORMEAUX A. ET AL: "Targeting HIV with liposome encapsulated antivirals" ZBL. BAKT., vol. 282, April 1995 (1995-04), pages 225-231, XP000980093 page 227, paragraph 3 page 229, paragraphs 1,2 ---	1-22
X	PHILLIPS N. C.: "Immunoliposome targeting to murine CD4+ leucocytes is dependent on immune status" J IMMUNOL, vol. 152, 1994, pages 3168-3174, XP000979265 see discussion abstract page 3169, column 1 --- -/--	1-18, 20-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/CA 00/00469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ZELPHATI O. ET AL: "Inhibition of HIV-1 replication in cultured cells with antisense oligonucleotides encapsulated in immunoliposomes" ANTISENSE RES DEV, vol. 3, 1993, pages 323-338, XP000979110 abstract page 325, paragraph 4 page 329 -page 331 ---	1-18, 20-22
X	DESORMEAUX A. ET AL: "Liposomes as drug delivery system: a strategic approach for the treatment of HIV infection" J DRUG TARGETING, vol. 6, no. 1, 1998, pages 1-15, XP000980031 abstract page 3, column 1, paragraph 2 -column 2 page 4, column 2, paragraph 2 page 6 -page 8; figure 1 ---	1-22
X,P	MARUYAMA K. ET AL: "Possibility of active targeting to tumor tissues with liposomes" ADV DRUG DELIV REVIEWS, vol. 40, 10 October 1999 (1999-10-10), pages 89-102, XP000980027 abstract; figure 5 page 96 ---	1-22
X	MENEZES DE D E L ET AL: "CELLULAR TRAFFICKING AND CYTOTOXICITY OF ANTI-CD19-TARGETED LIPOSOMAL DOXORUBICIN IN B LYMPHOMA CELLS" JOURNAL OF LIPOSOME RESEARCH,US,MARCEL DEKKER, NEW YORK, vol. 9, no. 2, May 1999 (1999-05), pages 199-228, XP000829355 ISSN: 0898-2104 abstract page 203 see discussion page 207, paragraph 3 ---	1-18, 20-22
T	LUNDBERG B. B. ET AL: "Specific binding of sterically stabilized anti-B-cell immunoliposomes and cytotoxicity of entrapped doxorubicin" INT J PHARMAC, vol. 205, September 2000 (2000-09), pages 101-108, XP000981286 abstract page 102, column 2, paragraph 2 page 106, column 2 -page 107 ---	1-18, 20-22

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2

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/CA 00/00469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
T	BESTMAN-SMITH J. ET AL: "Sterically stabilized liposomes bearing anti-HLA-DR antibodies for targeting the primary cellular reservoirs of HIV-1" BIOCHIM BIOPHYS ACTA, vol. 1468, 29 September 2000 (2000-09-29), pages 161-174, XP000980594 abstract see discussion page 163, column 2, paragraph 2; figure 1 ---	1-22
T	BESTMAN-SMITH J. ET AL: "Targeting cell-free HIV and virally infected cells with anti HLA-DR immunoliposomes containing amphotericin B" AIDS, vol. 14, 10 October 2000 (2000-10-10), pages 2457-2465, XP000980028 abstract see discussion page 2459 ---	1-22
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X	WO 96 25147 A (SEQUUS PHARM INC) 22 August 1996 (1996-08-22) page 15, line 3-13 page 15, line 30-33 page 11, line 11-34 ---	1-22
X	WO 96 10399 A (BERGERON MICHEL G ;DESORMEAUX ANDRE (CA)) 11 April 1996 (1996-04-11) abstract; claims 5,10; table 1 page 6, line 25-31 ---	1-22

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/CA 00/00469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 10585 A (INEX PHARMACEUTICALS INC) 11 April 1996 (1996-04-11) page 8, line 20 -page 9, line 20 page 15, line 15-20; claim 12; figure 1 page 12, line 7-9	1-22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-22

Present claims relate to an extremely large number of possible compounds/formulations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/formulations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Moreover the claims relate to a compounds defined by reference to a desirable characteristic or property, namely "ligand capable of binding to host membrane protein", and not a single claim fully defines the formulation
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds/formulations prepared in the examples and those variants specifically mentioned in the claims

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/CA 00/00469

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/CA 00/00469

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DH/11830.59		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00469	03/05/2000	03/05/1999
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant INFECTIO RECHERCHE INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/11/2000	17.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vogt, T Telephone No. +49 89 2399 8477

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00469

I. Basis f the r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-25 as originally filed

Claims, No.:

1-23 as received on 20/06/2001 with letter of 20/06/2001

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

I Amendments (Art. 41 PCT).

The applicant filed a new set of claims with the letter of 20.06.2001. The major amendment relates to the incorporation of claim 20 into claim 1. Minor amendments are made to claims 17 and 18 (incorporation of CD4).

Claims 22 and 23 were added.

Said amendments meet the requirements of Art. 41 (2) PCT.

II Priority (Art. 8 PCT).

The present application (with amended claim 1) validly claims the right to the filing date of CA application 2270600 (03.05.1999).

V Reasoned Statement. (Rule 66(2) PCT).

Subject matter of the present application.

The provision of a formulation comprising immunoliposomes optionally enclosing a drug for targeting an infectious agent which acquires at least one host membrane protein.

Cited prior art documents. (Rule 64(1) PCT).

D1: DESORMEAUX ET AL. (1995) ZBL. BAKT. 282, 225-231.
D2: PHILLIPS (1994) J. IMMUNOL. 152, 3168-3174.
D3: ZELPHATI ET AL. (1993) ANTISENSE RES. DEV. 3, 323-338.
D4: DESORMEAUX ET AL. (1998) J. DRUG TARGETING 6, 1-15.
D5: MARUYAMA ET AL. (10-1999) ADV. DRUG DELIV. REVIEWS 40, 89-102.
D6: MENEZES DE ET AL. (05-1999) J. LIPOSOME RES. 9, 199-228.
D7: LUNDBERG ET AL. (09-2000) INT. J. PHARMAC. 205, 101-108.
D8: BESTMAN-SMITH ET AL. (09-2000) BBA 1468, 161-174.
D9: BESTMAN-SMITH ET AL. (10-2000) AIDS 14, 2457-2465.
D10: DUFRESNE ET AL. (10-1999) BBA 1421, 284-294.
D11: US-A-5013556.
D12: EP-A-0286418.
D13: WO-A-9625147.
D14: WO-A-9610399. (cited in the description as US-A-5773027)

D15: WO-A-9610585.

D5, D6 and D10 will be considered as prior art according to Rule 33 (1) PCT insofar as they do not relate to the subject matter disclosed by the priority document.

D1 and D4 are reviews written by the authors of the present application relating to strategies using drugs loaded -liposomes (D1) and -immunoliposomes (D4) for the targeting of HIV infected tissues. D4 discloses the use of anti-CD4 antibodies conjugated to liposomes loaded with AZT to target to CD4+ lymphocytes (p. 6, 7). It further suggested to use these formulations for vaccinations, because of the observed increased immunogenecity in the presence of liposomes. D4 further contains references to the lipid composition of the liposomes (p. 3, l. 1-3), references to possible drugs to be enclosed in liposomes (p. 3, l. 40-43), discloses that sterically stabilized liposomes (eg. PEG-modified liposomes) increase the blood circulation time and visualizes the strategies in Figure 1.

D2 discloses anti-CD4 immunoliposomes optionally modified with PEG and optionally loaded with AZT to target to CD4+ PBMCs (peripheral blood mononuclear cells). The liposomes of the D2 are prepared from DPPC/DMPC (10/1) and are optionally substituted with 5% PEG_{1900}-PE (see materials and methods).

D3 discloses immunoliposomes loaded with antisense oligonucleotides to target to HIV infected T-lymphoblastoid cells. D3 discloses HLA-B and -C, CD7, and CD4 as possible targets for antibodies. (cf. p. 325; Antibodies, Cells and virus).
The examining authority is of the opinion that the subject matter of claims 1, 2, 10-18 and 22 does not meet the requirement of novelty over D3.

D5 relates to the use of loaded immunoliposomes to target cancer cells. It discloses that the pendant immunoliposome, also envisaged by the present application and illustrated in Fig. 1 of D4, is highly effective in targeting liposomes (Fig. 5).

D6 also relates to the use of loaded immunoliposomes to target cancer cells. It discloses the use of anti-CD19 antibodies, PEG, doxorubicin enclosed in the liposomes to target human B lymphoma cells. Because the disease cancer is not considered to be 'an infectious disease' D5 and D6 are not considered to be novelty destroying to the

present application.

D7, D8 and D9 are published after the filing date of the present application.

D10 discloses the subject matter covered by the priority document. Because it is the opinion of the examining authority that priority is validly claimed for this part of the application and D10 was published after (15.10.1999) the filing date of the priority document, the contents of D10 will be neglected.

D11 discloses sterically stabilized immunoliposomes for the targeting of HIV infected B or T cells. (cf. claims).

D12 discloses a method for targeting host cells infected by retroviruses (eg. HIV) using liposomes loaded with phosphorylated nucleotides (eg. AZT, DDC) and coated with an appropriate ligand (eg. anti-CD4). (cf. claims). The liposomes of D12 contain DPPC/DMPG in approximately 5/1 molar ratio.

D13 does not appear to contain information relevant to the present application.

D14 is written by the same inventors and discloses the lipid composition of the liposomes used in the present application.

D15 relates to the treatment of cancer with immunoliposomes.

Novelty and inventive step. (Art. 33(2,3) PCT).
As will have become clear from the above the idea of targeting liposomes that encapsulate drugs to specific tissues for the treatment of a disease is not novel. Also the idea of conjugating (parts of) antibodies to liposomes to increase the targeting efficiency thereof is not novel. Both, also apply for the application to infectious diseases such as AIDS.

However, none of the cited prior art documents mentions the use of ligands directed to HLA-DR. Therefore, claim 1 and all claims dependent thereon meet the requirement of novelty. (Rule 33 (2) PCT).

The technique as described in the present application and as first postulated almost two decades ago relies on the identification of an appropriate target on the outer-membrane leaflet of tissues (eg. a membrane protein). For the treatment of a disease this would imply membrane proteins directly or indirectly acquired as result thereof. About one decade ago it was discovered that the membrane protein HLA-DR is acquired as a result of HIV infection (see references 23, 24 in D8; 29 in D9 and p. 2 , l. 9-24 of the priority document). Hence it would appear that HLA-DR is an obvious target for such a strategy. However, despite the fact that the field of drug targetting has been booming over the last decade nobody has made the link towards the use of HLA-DR. Furthermore HLA-DR is a particular interesting target, because it is not only aquired by a host cell as a result of an infection it is also displayed by the infectious agent itself.

Hence, the subject matter of claims 1-21 of the present application meets the requirements of inventive step (Rule 33 (3) PCT).

Also the inventive step of claims 22 and 23 is acknowledged, based on the fact that the present application is the first to suggest the use of ligands that are aimed to target to a host cell receptor that is present on **both** the infected cell **and** the infectious agent.

Industrial applicability. (Art. 33(4) PCT).
The present application provides formulations for treatment of infectious diseases. The subject matter meets the requirement of industrial applicability.

VII Remarks related to the description (Art. 5 PCT).

The description should be brought into conformity with the amended claims.

The applicant should identify documents D2, D3, D4, D8, D9, D11 and D12 in the description. (Rule 5 PCT).

VIII Clarity of the claims (Art. 6 PCT).

Claims 7-9 are not conform the description on p. 7 and 8. The applicant is requested to amend the description or claims accordingly.

The vague and imprecise statement in the description on p. 25, l. 11-13 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
DH/11830.59		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00469	03/05/2000	03/05/1999
Applicant		
INFECTIO RECHERCHE INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

TARGETING OF INFECTIOUS AGENTS BEARING HOST CELL PROTEINS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-22

Present claims relate to an extremely large number of possible compounds/formulations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/formulations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Moreover the claims relate to a compounds defined by reference to a desirable characteristic or property, namely "ligand capable of binding to host membrane protein", and not a single claim fully defines the formulation
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds/formulations prepared in the examples and those variants specifically mentioned in the claims

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00469

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DESORMEAUX A. ET AL: "Targeting HIV with liposome encapsulated antivirals" ZBL. BAKT., vol. 282, April 1995 (1995-04), pages 225-231, XP000980093 page 227, paragraph 3 page 229, paragraphs 1,2 ---	1-22
X	PHILLIPS N. C.: "Immunoliposome targeting to murine CD4+ leucocytes is dependent on immune status" J IMMUNOL, vol. 152, 1994, pages 3168-3174, XP000979265 see discussion abstract page 3169, column 1 --- -/--	1-18, 20-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ZELPHATI O. ET AL: "Inhibition of HIV-1 replication in cultured cells with antisense oligonucleotides encapsulated in immunoliposomes" ANTISENSE RES DEV, vol. 3, 1993, pages 323-338, XP000979110 abstract page 325, paragraph 4 page 329 -page 331 ---	1-18, 20-22
X	DESORMEAUX A. ET AL: "Liposomes as drug delivery system: a strategic approach for the treatment of HIV infection" J DRUG TARGETING, vol. 6, no. 1, 1998, pages 1-15, XP000980031 abstract page 3, column 1, paragraph 2 -column 2 page 4, column 2, paragraph 2 page 6 -page 8; figure 1 ---	1-22
X,P	MARUYAMA K. ET AL: "Possibility of active targeting to tumor tissues with liposomes" ADV DRUG DELIV REVIEWS, vol. 40, 10 October 1999 (1999-10-10), pages 89-102, XP000980027 abstract; figure 5 page 96 ---	1-22
X	MENEZES DE D E L ET AL: "CELLULAR TRAFFICKING AND CYTOTOXICITY OF ANTI-CD19-TARGETED LIPOSOMAL DOXORUBICIN IN B LYMPHOMA CELLS" JOURNAL OF LIPOSOME RESEARCH,US,MARCEL DEKKER, NEW YORK, vol. 9, no. 2, May 1999 (1999-05), pages 199-228, XP000829355 ISSN: 0898-2104 abstract page 203 see discussion page 207, paragraph 3 ---	1-18, 20-22
T	LUNDBERG B. B. ET AL: "Specific binding of sterically stabilized anti-B-cell immunoliposomes and cytotoxicity of entrapped doxorubicin" INT J PHARMAC, vol. 205, September 2000 (2000-09), pages 101-108, XP000981286 abstract page 102, column 2, paragraph 2 page 106, column 2 -page 107 ---	1-18, 20-22

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
T	BESTMAN-SMITH J. ET AL: "Sterically stabilized liposomes bearing anti-HLA-DR antibodies for targeting the primary cellular reservoirs of HIV-1" BIOCHIM BIOPHYS ACTA, vol. 1468, 29 September 2000 (2000-09-29), pages 161-174, XP000980594 abstract see discussion page 163, column 2, paragraph 2; figure 1 ---	1-22
T	BESTMAN-SMITH J. ET AL: "Targeting cell-free HIV and virally infected cells with anti HLA-DR immunoliposomes containing amphotericin B" AIDS, vol. 14, 10 October 2000 (2000-10-10), pages 2457-2465, XP000980028 abstract see discussion page 2459 ---	1-22
X,P	DUFRESNE I. ET AL: "Targeting lymph nodes with liposomes bearing anti-HLA-DR Fab' fragments" BIOCHIM BIOPHYS ACTA, vol. 1421, 15 October 1999 (1999-10-15), pages 284-294, XP000980066 abstract; figure 1 see discussion page 287 ---	1-22
X	US 5 013 556 A (REDEMANN CARL T ET AL) 7 May 1991 (1991-05-07) column 12, line 28-30 column 12, line 54-64; claims 1,17,32,33 ---	1-22
X	EP 0 286 418 A (US GOVERNMENT) 12 October 1988 (1988-10-12) claims 6-8; examples 1,3 ---	1-18, 20-22
X	WO 96 25147 A (SEQUUS PHARM INC) 22 August 1996 (1996-08-22) page 15, line 3-13 page 15, line 30-33 page 11, line 11-34 ---	1-22
X	WO 96 10399 A (BERGERON MICHEL G ;DESORMEAUX ANDRE (CA)) 11 April 1996 (1996-04-11) abstract; claims 5,10; table 1 page 6, line 25-31 ---	1-22

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 10585 A (INEX PHARMACEUTICALS INC) 11 April 1996 (1996-04-11) page 8, line 20 -page 9, line 20 page 15, line 15-20; claim 12; figure 1 page 12, line 7-9 -----	1-22

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Information on patent family members

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PCT/CA 00/00469

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